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EXAMINER	
BETTON, TIMOTHY E	
ART UNIT	PAPER NUMBER
1617	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,552	ZELDIS, JEROME B	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *11,12 and 26-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 13-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :8 sheets, 6/15/2007, 1 sheet 12/10/2008.

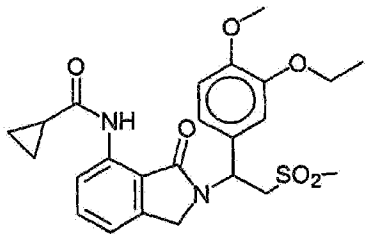
DETAILED ACTION

Applicants Election by Phone

During a telephone conversation with Anthony Insognia on 18 November 2008 a provisional election was made without traverse to prosecute the invention of Group I, claims. Affirmation of this election must be made by applicant in replying to this Office action. Claims 26-37 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. The current claims read on the current invention: 1-10 and 13-25.

Applicants elect:

Cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide has the following chemical structure:



As the cytokine inhibitory drug species.

The attorney has also noted that the SO2- should read SO2Me.

Claim 11 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected claims, being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 18 November 2008.

Subsequently, the applicants elect the racemate of said cytokine inhibitory drug species. Applicants' elect dexamethasone as the second agent. *Applicants' further elect the primary stage of the disease myelodysplastic syndrome which encompasses* refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, or chronic myelomonocytic leukemia.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-25 are drawn to a method of treating or preventing a myelodysplastic syndrome

Group II, claim(s) 26-37 is drawn to a pharmaceutical composition, a single unit dosage form, and a kit comprising a selective cytokine inhibitory drug.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The method of treating or preventing a myelodysplastic syndrome may be practiced with different active agents (please see Raza et al (Pentoxifylline, Ciproflaxacin, and Dexamethasone Improve the Ineffective Hematopoiesis in Myelodysplastic Syndrome Patients; Malignancy, Hematology, 2000; 5(4): 275-284). The compound/composition is known to fully substantiate the restriction away and apart from the

methods as disclosed. Likewise, the same compound/composition can be used in a different process or methods of treatment also. However, in the case of the Raza et al. reference, different active agents can be used in the same process as elected.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

(a) a cytokine inhibitory drug species

(b) second ingredient species primary or secondary (claim 9)

(c) R or S enantiomer

(d) blood species according to claim 36

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The claims are deemed to correspond to the species listed above in the following manner:

Claims 1-4, 15, 17, 19, 21 are drawn to a cytokine inhibitory agent species

Claims 5-8, 24, and 25 are drawn to a second agent

Claim 9 is drawn to a particular stage of myelodysplastic syndrome.

The following claim(s) are generic: 1-5, 6-9, 15, 17, 19-22, 24-27, and 29-37. Please state which claims are withdrawn from further consideration and why.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Methods of treating and prevention a myelodysplastic syndrome may be treated with a therapeutically effective amount of other agents.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4-10 and 13-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating myelodysplastic disorders, does not reasonably provide enablement for preventing and/or myelodysplastic disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims

Factors to be considered determining whether a disclosure would require undue experimentation have been summarized in Exparte Forman, 230 USPQ 546 (BPAI 1986) and

reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include:

1) the quantity of experimentation necessary
2) the amount of direction or guidance provided
3) the presence or absence of working examples
4) the nature of the invention
5) the state of the art
6) the relative skill of those in the art
7) the predictability of the art and
8) the breadth of the claims

Firstly, with regard to the limitation drawn to claims 2-4, which each disclose *a prophylactically effective amount,* the specification is silent with regard to what is meant by *a prophylactically effective amount* .Therefore, in the absence of a proposed definition in the specification, the limitation is broadly interpreted to include prevention.

Claim 4 does not specifically disclose prevention but based on the alleged scope of the invention, the limitation drawn to *a prophylactically effective amount* may be reasonably interpreted and extended to encompass prevention.

Breadth of the claims, state of the art and nature of the invention

Gore et al. Future Directions in Myelodysplastic Syndrome: Newer Agents and the Role of Combination Approaches, Cancer Control (2008), vol. 15, no.4, supplement, printed pages 1-49 teach that Myelodysplastic Syndrome (MDS) is not a single disease, but a collection of hemopoietic disorders that require newer strategies (abstract only, lines 1 and 2). The breadth of the claims suggests art-known agents in combination for the said progressive disorder,

MDS. The nature of the invention suggests that the disclosed treatment of a cytokine inhibitory drug and dexamethasone in combination will be sufficient in order to prevent MDS.

Predictability/unpredictability of the art and Quantity of due experimentation necessary

Gore goes on to cite that [...] the development of new strategies remains critical, and because MDS includes biologically heterogeneous diseases, one strategy will not likely benefit all patients, pg. 41. Thus, predictability is not certain based on the limitations cited within the current invention and the current specification. The quantity of experimentation would be extensive in view of the disclosure of Gore et al. and accordingly in view of the content and the lack thereof found within the Examples 1-3. The Examples fail to describe a distinct embodiment which would reasonable suggest that prevention of MDS is enabled in view of other variable therapies as cited by Gore et al. that at best only suggest on-going efficacious treatment for the disorders and etiologies of MDS. Further, the examples cite studies drawn to evaluating the efficacy and safety of the oral administration of a cytokine inhibitor. However, there is no embodiment drawn to the enablement of prevention as claimed in view of the safety and efficacy profile.

The Amount of Direction or Guidance Provided

Gore et al. cites combination therapy and the rationale, published experience, and ongoing studies in the management of MDS.

The current specification cites that [e] mbodiments of the invention described herein are only a sampling of the scope of the invention. The full scope of the invention is better understood with reference to the attached claims (page 41).

However, the claims as disclosed do not sufficiently support or suggest prevention of MDS via direction and/or guidance drawn to such cumulative and/or correlative data comprising 1) increased response rates 2) prolonged response duration 3) decreased toxicities associated with treatment 4) combining agents based on an understanding of convergent or complementary moleculer mechanisms with *in vitro* or *in vivo* evidence of synergy 5) survival rates 6) disclosure suggesting prevention based on mechanistically related combination of such agents fully supported and based on models of epigenetic biology (page 44).

The specification cites on page 26 in 4.3 Methods of Treatment and Management. The limitation drawn to prevention includes but is not limited to the inhibition or the averting of symptoms associated with MDS. However, the suggestion that the applicants make with regard to prevention is also absent with regard to inhibition or the averting of symptoms. The target population is not individualized in such a way that treatment of the variable symptoms and stages are properly addressed. Based on applicants' definition of prevention, it is still not evident in the specification of claims that inhibition or aversion of some remarkable degree has been achieved in order to determine treatment for all etiological representations of MDS.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 15-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for treating myelodysplastic syndrome with some selective

cytokine inhibitory agents, does not reasonably provide enablement for treating any myelodysplastic syndrome disorder as disclosed with any selective cytokine inhibitory agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. (Please see specification, pp. 38-41, Examples 1 begins on page 39, specifically. Examples 2 and 3 on page 40 cite two distinct studies).

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Exparte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include:

1) the quantity of experimentation necessary
2) the amount of direction or guidance provided
3) the presence or absence of working examples
4) the nature of the invention
5) the state of the art
6) the relative skill of those in the art
7) the predictability of the art and
8) the breadth of the claims

Breadth of the claims, state of the art and nature of the invention

Gore et al. Future Directions in Myelodysplastic Syndrome: Newer Agents and the Role of Combination Approaches, Cancer Control (2008), vol. 15, no.4, supplement, printed pages 1-49 cite on page 42, second paragraph, line 6 that what is referred to as the *cytokine milieu* is listed among other forms of needed modulation in order to reasonably affect improvement.

Mocharnuk, R. (Myelodysplasia: An Age-Old Problem, Scripps Cancer Center's Annual Conference: Clinical Hematology and Oncology, (2002), printed pages 1-4 teach the nature of the invention and state of the art at the time of claimed invention.

Specifically, Mocharnuk teaches Myelodysplastic syndrome (MDS) is a difficult disease to tackle for a number or reasons, including problems with classification systems, a marked tendency to affect older patients less tolerant of aggressive treatments, and a lack of standard treatment options. Dr. Robert Petitt, [1] from the Mayo Clinic in Rochester, Minnesota, discussed these and other troublesome issues in a comprehensive review of state-of-the-art MDS management. MDS is a clonal disease of hematopoietic stem cells, characterized by ineffective erythropoiesis and cytopenias, often leading to the development of acute leukemia. The incidence of MDS increases with age, with a median age at diagnosis of 69 years. Among individuals between the ages of 50 and 70 years, 4.9 of every 100,000 develop MDS, while the incidence among those older than 70 years rises to 22.8 per 100,000 (page 1, first and second paragraphs).

Further Mocharnuk teaches for now, the management of MDS must continue to be individualized, taking into account the patient's age, performance status, comorbid conditions, IPSS score and availability of marrow donors (page 4, last paragraph).

The breadth of the claims support and suggest that a particular subset of chemotherapeutic agents such as cytokine inhibitory agents are sufficient in treating the myriad disorders associated with MDS but Mocharnuk cites that [a]gents that stimulate cellular differentiation are numerous, but none have produced the levels of response that would designate them as

"standards of care." In turn, levels of response drawn to cytokine inhibitors principally in the claimed invention to treat a plethora of etiological disorders associated with MDS do not seem to support or suggest a "standard of care" as intended.

Predictability/unpredictability in the art and Quantity of due experimentation necessary

Gore et al. cites that the goal of pharmacotherapy in the management of MDS is to increase the overall survival of the patient. Gore et al. goes on to disclose that the overall survival in response to [one agent] compared with conventional care regimens (addressing cumulative and correlative data, i.e., CR, PR, and HI) is encouraging, [but] still may not be adequate to provide a complete picture of the positive treatment in MDS patients (Conclusions, lines 1-8). This disclosure clearly suggests that based on state of the art disclosed *supra,* unpredictability is high and that routine experimentation requires data that correlates with the use of the compounds and compositions as disclosed.

The Amount of Direction or Guidance Provided

The direction and guidance provided does not support or suggest the claims of the invention. The treatment of all such disorders represented by MDS is not clearly delineated in the specification or the claims. The direction and guidance are drawn more to safety and efficacy trials as incorporated by the FDA than with regard to any scope of enablement drawn to the treatment of MDS syndrome *inter alia* with the compounds and compositions as disclosed.

Accordingly, the application adequately teaches embodiments drawn to data for *one* specific agent which contrasts significantly with regard to the broad scope of *any* selective

cytokine inhibitor. The amount of direction is deficient in view of the variable selective cytokine inhibitors disclosed. Selective cytokine inhibitors comprise a very broad scope of agents which would not necessarily exhibit the same mechanisms of action and/or exhibit the same properties and characteristics.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1- 10 and 13-25 are provisionally rejected on the ground of nonstatutory double patenting over claims 46-49, 53-54 and 65 of copending Application No. 11/ 250, 408. The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: Claims 1-10 and 13-20 of current claim set disclose a chemical entity that reasonably teaches the chemical entity as disclosed in the copending application. Additionally, the claims drawn to methods reasonably encompass the methods of treatment for blood-born cancers and specifically for MDS (claim 65).

The cited claims of the co-pending application are determined to encompass the scope and content of the current application. Claims 46-48 disclose the elected compound. Claim 49

discloses an additional agent comprising a steroid, which reasonably is interchangeable with dexamethasone as the elected second agent of the current invention. Claims 53-54 disclose methods drawn generally to the disorder MDS, i.e., blood-born cancer. Claim 65 discloses the limitation drawn to treatment for MDS.

Claims 1- 10 and 13-25 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-10, 13-21 and 25-29 and 41 of copending Application No. 11/ 818,927. The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: Claims 1-10 and 13-20 of current claim set disclose a chemical entity that reasonably teaches the chemical entity as disclosed in the copending application. Claim 41 of the said co-ending application specifically teach a method of treating, preventing, and managing Myelodysplastic syndrome in a patient [...].

The cited claimed of the said co-pending application are determined to encompass the scope and content of the current application. Claims 1-10 disclose embodiments drawn to variations of the chemical groups of the title formula including the elected compound of current invention. Claims 13-18 disclose further embodiments drawn to the variation of the title formula including the elected compound of current invention. Claims 19- 21 teach an additional agent which is taught in the current application in claim 13 as the second agent. Claim 21 discloses a steroid which is reasonably interchangeable with dexamethasone as the second agent in the current invention. Claims 25-29 disclose methods of treatment which clearly read on the methods of treatment of the current invention. Claim 41 specifically teach a method of treatment *inter alia* for MDS.

The differences in the co-pending applications and the current application are that limitation of an additional agent such as a steroid is not expressly named. However, it would reasonable within the purview of the one of skill to try dexamethasone as a secondary/ additional agent.

The objective obviousness present in current application is the essential congruence between the chemical entities of the said co-pending applications and the compound as elected. Further objective evidence of obviousness is drawn to the specific disease state that is treated among both co-pending application and the current invention at issue.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claims 1-10 and 15-20 are rejected on the ground of nonstatutory double patenting over claims 1-15 of U. S. Patent No. 6020358, since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: claim 1: The sulfone selected from the group consisting of (a) a compound of the formula.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804. we rarely use this form paragraph. Use a form paragraph from 8.34-8.37.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 15-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al., (USPN 6, 020,358) and Muller et al (USPN 5,658,940) in view of Raza et al (Pentoxifylline, Ciproflaxacin, and Dexamethasone Improve the Ineffective Hematopoiesis in Myelodysplastic Syndrome Patients; Malignancy, Hematology, 2000; 5(4): 275-284. Muller et al. (USPN 358) teach the chemical entity represented as a phenethylsulfone compound of Formula I which is congruent with the chemical moiety in the claimed invention) (please see col. 5, lines 1-12), *but does not fairly teach the elected compound.*

Muller et al. (USPN '940) teach the use of the steroid dexamethasone that is also used in the controlling and/or inhibiting the production or action tumor necrosis factor α.

Muller et al. (USPN '940) teach cancer (col. 3, line 25)

Muller et al. ('358 and '940) do not teach the formulation expressly drawn toward a treatment for myelodysplastic syndrome.

Raza et al. teach:

> Twenty-five patients with a diagnosis of myelodysplastic syndromes (MDS) were randomized to either begin therapy with pentoxifylline, ciprofloxacin and dexamethasone (PCD) immediately (10 patients) or after a 12 week observation period (control arm, 15 patients). PCD was administered with the goal of suppressing cytokine-induced excessive intramedullary apoptosis of hematopoietic cells. No marked fluctuations of blood counts were noted during the period of observation. Twenty-two patients completed at least 12 weeks of therapy: 18/22 showed some type of hematologic response, 9/18 showing an improvement in absolute neutrophil count only ($p = < 0.001$) and 9/18 showing multi-lineage responses. No unique category of MDS responded better, however 19/25 patients had refractory anemia (RA)/RA with ringed sideroblasts. The median time to response was 6 weeks and 3/18 responding patients maintained their responses beyond a year. We conclude that hematologic improvement in response to PCD therapy supports the validity of this unique anti-cytokine approach. Future trials should combine PCD therapy with established approaches (growth factors/chemotherapy) and also should focus on identifying more effective ways of suppressing the pro-apoptotic cytokines in MDS.

Thus, Raza et al. teach the use of dexamethasone for the direct treatment of myelodysplastic syndrome in the absence of any chemotherapeutic agent such as a cytokine inhibitor agent.

The deficiency in Raza et al. and the Muller references *supra* are resolved via the disclosure of the CELGENE CORP/DE/-10-K Annual Report, 12/31/2000, printed pages 1-165 which clearly indicates the treatment of myelodysplastic anemia with selective cytokine inhibitors (SelCID's) (p.5, 3rd ¶, L.3; p.6, 1st ¶, p.8 1st class of agents, 1st column).

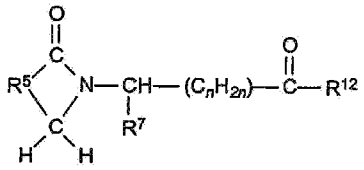
CELGENE teach MDS (p. 18, last ¶, L.1; p. 19, 1st ¶, L.1 and 4).

Thus, the disclosure of CELLGENE CORP adequately and clearly teach SelCIDs in clinical studies involving MDS.

Claim 1-10, 15-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al., (USPN 6, 020,358) and Muller et al (USPN 5,658,940) in view of Raza et al (Pentoxifylline, Ciproflaxacin, and Dexamethasone Improve the Ineffective Hematopoiesis in Myelodysplastic Syndrome Patients; Malignancy, Hematology, 2000; 5(4): 275-284 as applied to claim above, and further in view of Muller et al (USPN 5,605,914) .

Muller et al. ('914) teach the chemical moiety as represented in claim 15. Muller et al. teach this cytokine inhibitor/cyclic imide in column 6, lines 15-18, structure IIA. Muller et al. also teach the limitation of dexamethasone used as adjunctive treatment as a steroid in the administration to inhibit the production of TNFα.

The generic compound:



Thus, it would have been *prima facie* obvious to the one of skill at the time of invention to, at once, recognize a reasonable expectation of success via incorporating together the methods and teachings of the Muller et al. references, Raza et al. and CELGENE CORP. as disclosed.

Raza et al. provides the motivation to combine based on the teachings of Muller et al. directed to combination therapy with dexamethasone.

The scope and contents of the prior art are commensurate with the scope and content of the claimed invention. Cytokine inhibitors are art-known chemical entities in the treatment of variable blood-type cancers comprising MDS. CELLGENE CORP clearly discloses the intended use for the compound as elected called SelCIDs in the pertinent art.

The differences between the prior art and the claims at issue are the lack of congruent similarity between the elected compound and the compounds of the Muller et al. references. The elected compound contains a variation in the constituents on the general structure a representative 7 amido-substituted isoindolyl compound

The objective evidence present indicating obviousness are teachings drawn to the art-known therapeutic activity of SelCIDs for various disorders etiologically similar and encompassing the disorders associated with MDS. The second agent, dexamethasone is also art-known as disclosed above in association with the adjunctive treatment of such disorders.

The elected species is free from the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Shengjun Wang/

Primary Examiner, Art Unit 1617